



Residents' Case Series

A 14-year-old Girl with Refractory Seizures

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A 14-year old Micronesian female with no significant past medical history presented to the emergency department with tonic-clonic seizures. Earlier in the evening, the patient went to the movies with her family and was in her usual state of health. The patient had a history of dental caries and had a toothache that evening. When getting ready for bed, she received permission from her mother to take another family member's medication to self-treat the tooth pain. Within an hour of taking the medication, the patient's mother heard a loud cry from the patient's room. At that time, the patient was found to be having a generalized tonic-clonic seizure. An ambulance was called, and when the paramedics arrived, she was unresponsive and still actively seizing. She was given diazepam 3.5 mg intravenously without effect. She was given another 3.5 mg of diazepam and the seizure resolved. The total time of the seizure was approximately thirty minutes. The patient was transported to the emergency department, remained unresponsive and began seizing again upon her arrival.

The patient had no significant past medical history except dental caries. She was born by normal spontaneous vaginal delivery in the Marshall Islands. Her prenatal and postnatal courses were unremarkable. She had no previous hospitalizations, no surgeries, no allergies and was on no routine medications. Her immunizations were up to date. She had no recent travel, no exposure to toxins or pets, did not smoke cigarettes, drink alcohol or take illicit drugs, and had no significant family medical history. She was one of six children, ages ranging from 2 to 22 years. Her parents were divorced, and the children lived with their mother. Her family stated that except for the toothache, she was perfectly well earlier that evening without any complaints of trauma, headache, neck stiffness, photophobia, fever, rash or other problems. The medication she had taken for her tooth pain belonged to a family member.

On physical exam, the patient was initially unresponsive and having generalized tonic-clonic seizures. Her vital signs included: heart rate 155 beats per minute; blood pressure 133/61; temperature 100.2 tympanic; oxygen saturation 100% while receiving assisted respirations and 100% oxygen. There were no obvious rashes or signs of trauma. Her pupils were 4 mm and equal and reactive to light. Her lungs were clear and her cardiac exam was normal except for tachycardia. Her abdomen was soft, bowel sounds were present. Her extremities were normal. When the seizures had stopped, she remained unresponsive and had nonpurposeful movements of all extremities.

Laboratory studies obtained in the emergency department revealed: A white blood count of $26.7 \times 10^9/L$ with 68% neutrophils and 32% lymphocytes; hemoglobin 12.5 g/dL and hematocrit 36.7%; platelets 322,000. Chemistries included: sodium 139 mmol/L (136-145); potassium 3.0 mmol/L (3.3-5.1); chloride 103 mmol/L (96-108); bicarbonate 8 mmol/L (21-31); anion gap 28 (4-16); BUN 8 mg/dL (6-19); Cr 0.9 mg/dL (0.4-1.1); glucose 302 mg/dL (70-

110); calcium 9.1 mg/dL (8.4-10.2); phosphorus 5.9 mg/dL (2.6-4.5). Liver function tests were within normal limits. An arterial blood gas on 100% oxygen showed pH 7.19, pCO₂ 38, pO₂ 504, bicarbonate 15, base excess -12. A urine toxicology screen was negative for illegal drugs. A urine pregnancy test was also negative. Blood salicylate and acetaminophen levels were negative. A CT scan of the head did not show any bleeding or masses.

The medication that the patient took for her toothache was brought to the emergency department by the paramedics. It was a regular pharmacy prescription bottle labeled "amoxicillin". The contents of the bottle were inspected and two different types of pills were noted. The first type was identified as amoxicillin, the other was isoniazid.

The patient continued to seize. She was given phenytoin and phenobarbital to control her seizures, and she was intubated. At this point, isoniazid toxicity was suspected, so the patient was given 5 grams of pyridoxine IV and activated charcoal. An isoniazid level was obtained and later found to be 54.4 mcg/ml (toxic level is greater than 10 mcg/ml). An EEG showed a diffuse encephalopathic process with high amplitude delta wave and no seizure discharges. The patient remained unresponsive and intubated in the pediatric intensive care unit for ten days. On her tenth hospital day, she became arousable and fairly quickly became responsive. She ultimately fully recovered and was discharged home.

Discussion

Isoniazid (INH) was introduced in 1952; it is the hydrazide of isonicotinic acid. It is used for tuberculosis (TB) either as preventative therapy or for active disease in combination with other medications.¹ The incidence of isoniazid toxicity in the pediatric population is unknown; however, toxic events involving this medication have increased as this medication is used with increasing frequency. With the resurgence of tuberculosis in HIV-infected patients and recent immigrants from areas with endemic TB, INH usage has increased.² The State of Hawaii has a high per-capita rate of TB and people immigrating from the Pacific Islands and Asia, where the prevalence of TB is high, have contributed to the high rate here. Consequently, INH use in Hawaii has also increased as therapy for active disease or prophylaxis.

In children, the usual dose of INH is 10-15 mg/kg in contrast with doses of 5 mg/kg in adults. Neurotoxicity and seizures can occur with ingestion of 40 mg/kg or less.³ INH is 95% bioavailable and effects after a toxic dose are usually seen within 30 minutes to 2 hours of ingestion.² Therapeutic doses in children result in peak blood levels of 6-20 mg/ml. Toxic levels are greater than 10 mg/ml, or 3.2 mg/ml two hours after ingestion, 0.2 mg/ml 6 hours after ingestion.³ INH is metabolized by acetylation and excreted chiefly in the urine. The half-life depends on the acetylation status of the patient which is a genetically determined factor. The half-life in "fast" acetylators is approximately 90 minutes or less, and 180 minutes in "slow" acetylators.¹ It is estimated that 60% of Caucasians and African-Americans are slow acetylators and 10% of Asian-American and Alaskan natives are slow acetylators.⁴

Iatrogenic overdose of INH while taking the medication as directed is rare. One case described took place in a patient thought to be a slow acetylator; with the medication half-life doubled, it was hypothesized that toxic levels were achieved while on therapeutic doses.

Most acute toxic events from INH come from either suicide attempt or accidental ingestion, as with our patient. Another case in Hawaii involved a teenage girl who ingested a large quantity of INH in a suicidal gesture after a fight with her boyfriend; she suffered a seizure and was brought to the hospital by ambulance. One case-series from Los Angeles involved three siblings and a possible accidental overdose: a four-year old child was prescribed INH for a positive PPD and his two younger siblings, ages 2 1/2 and 1 1/2 years, were brought to the medical facility with generalized convulsions.⁵ Another pediatric overdose occurred when an infant was prescribed 300 mg INH daily rather than 30 mg daily.³ One author (Byron Aoki) saw long term complications in children with INH-induced seizures in the 1970's who were not treated with pyridoxine. They developed permanent neurologic damage in cognition and behavior.

The classic clinical presentation of acute INH toxicity includes the triad of refractory seizures, coma and metabolic acidosis. Other features consist of slurred speech, ataxia, hypotension, fever, peripheral neuritis, nausea and vomiting, hypokalemia, leukocytosis, hyperglycemia with ketonuria and glycosuria.^{5,6,7} It is important that the anion gap acidosis coupled with the hyperglycemia does not get mistaken for diabetic ketoacidosis.³ Our patient had many of these features including refractory seizures, coma, wide anion gap metabolic acidosis, leukocytosis, hypokalemia and hyperglycemia.

The mechanism of seizures in INH toxicity is thought to be due to a depletion of the inhibitory neurotransmitter γ -aminobutyric acid (GABA).³ Decreased levels of GABA can result in CNS excitability and seizures. The synthetic pathway for GABA involves glutamic acid decarboxylase. Pyridoxine (vitamin B6) is activated to pyridoxal-5-phosphate which is a cofactor for glutamic acid decarboxylase. INH, in overdose, binds free pyridoxal-5-phosphate, which acutely lowers this cofactor necessary for GABA synthesis, which results in a seizure.³

The treatment of INH overdose includes the management of life-threatening symptoms, administration of pyridoxine and supportive care.⁶ The initial management includes airway control, maintenance of respirations, and ensuring adequate circulation; this may require endotracheal intubation, intravenous access and intravenous fluids. To stop seizures in children, diazepam 0.1-0.2 mg/kg or lorazepam 0.05-0.1 mg/kg can be given and repeated as needed. Diazepam is thought to be more effective than other anticonvulsants in treating INH-induced seizures, perhaps acting with a synergistic effect with pyridoxine.⁸ Pyridoxine should be given intravenously as soon as possible. The pyridoxine dose should be the same dose of INH that was taken (one gram of pyridoxine for every one gram of INH ingested);^{7,8} if the amount INH ingested is not known, 5 grams of pyridoxine IV over 5-10 minutes should be sufficient in most cases.⁷ If ingestion has occurred within an hour, gastric lavage can be performed followed by 15-30 grams (1-2 g/kg) of charcoal with 1-1.5 grams/kg of sorbitol (up to 50 grams) as a slurry for children. The charcoal dose without the sorbitol can be repeated. If these measures do not control the seizures, hemodialysis may be necessary.

Isoniazid is the fourth leading cause of drug-induced seizures accounting for approximately 5% of all seizures associated with overdose. This is likely to increase following the rise in TB in our community. In our patient, examination of the medication taken indicated this was likely an INH overdose. When the preceding

history is not clear, the possibility of INH toxicity must be strongly considered in any case of refractory seizures with metabolic acidosis. Treatment with pyridoxine must be considered as it can dramatically alter the patient's outcome. Finally, emergency departments must be sure that enough pyridoxine is available for treatment.

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